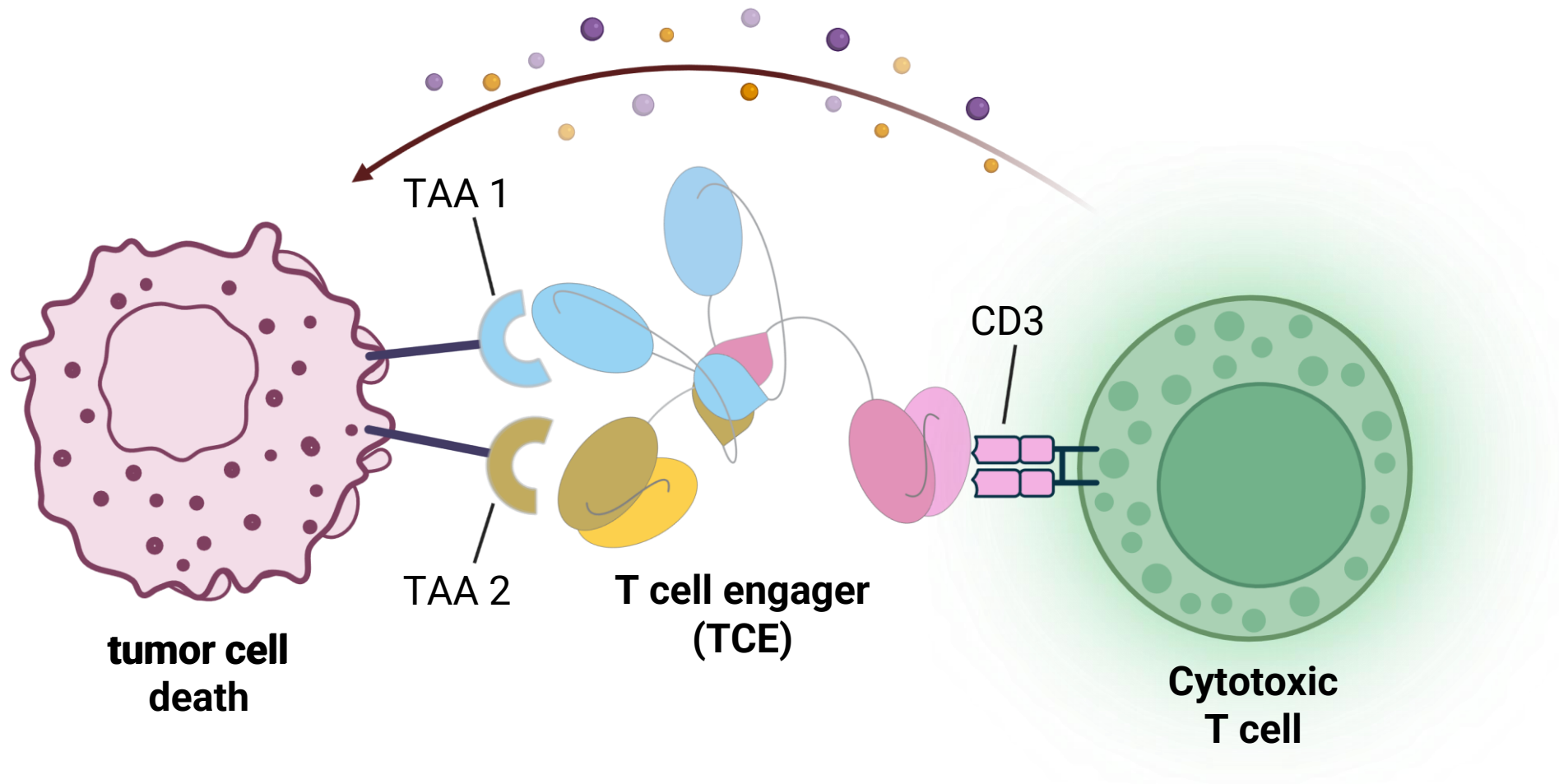


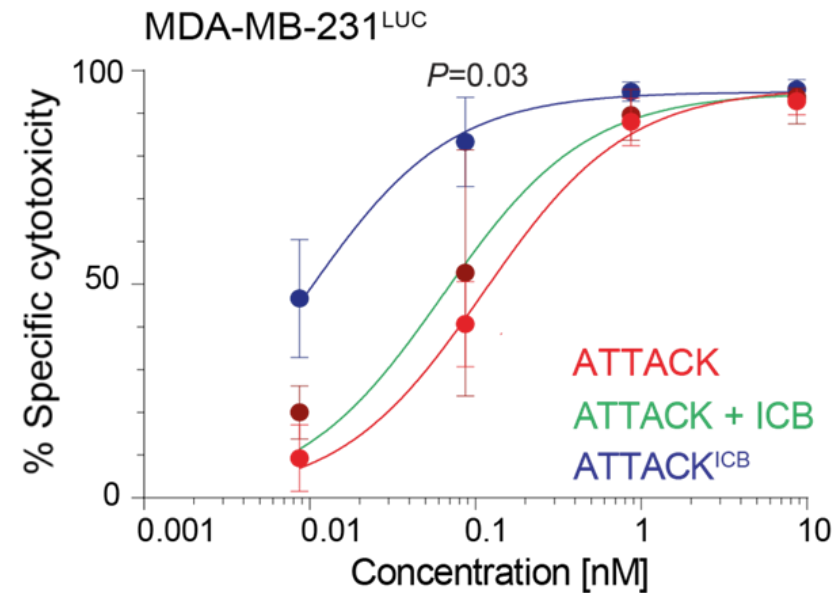
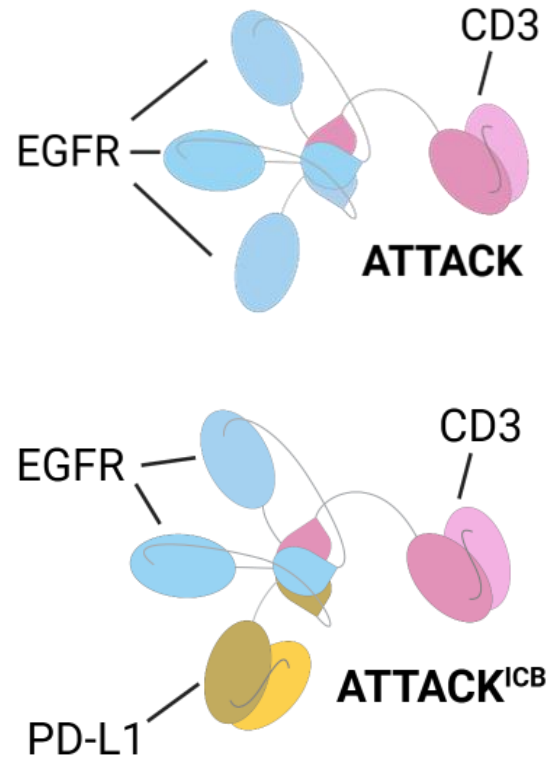
Anti-tumor activity of an RNA-encoded *in situ* produced trispecific antibody combining T-cell engagement and local checkpoint inhibition

Philipp Lapuhs, Ivana Zagorac, Rocío Navarro, Antonio Tapia-Galisteo, Marta Compte, Belen Blanco, Laura Sanz, Luis Álvarez-Vallina, María José Alonso

Therapeutic potential of T cell engagers



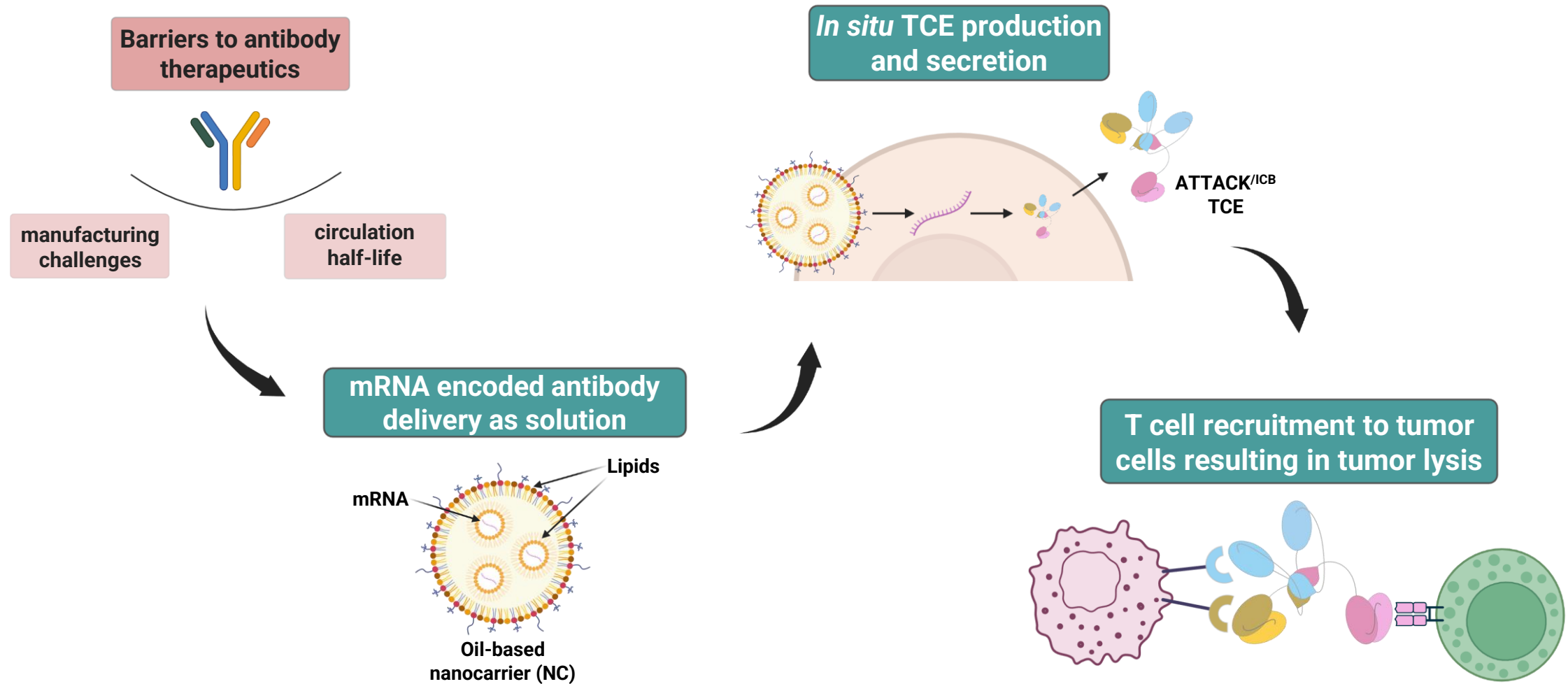
TCE design and functional evaluation



ATTACK^{ICB} exhibits functional multi-specificity and superior cytotoxic activity

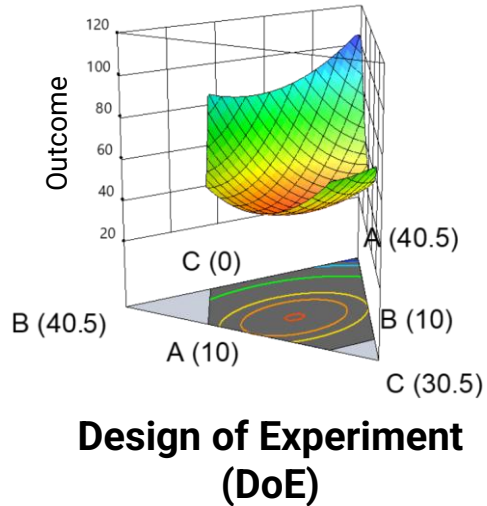
ATTACK: *A*symmetric *T*andem *T*rimerbod**y** for *T* cell *A*ctivation and *C*ancer *K*illing

Nanotechnology as enabler

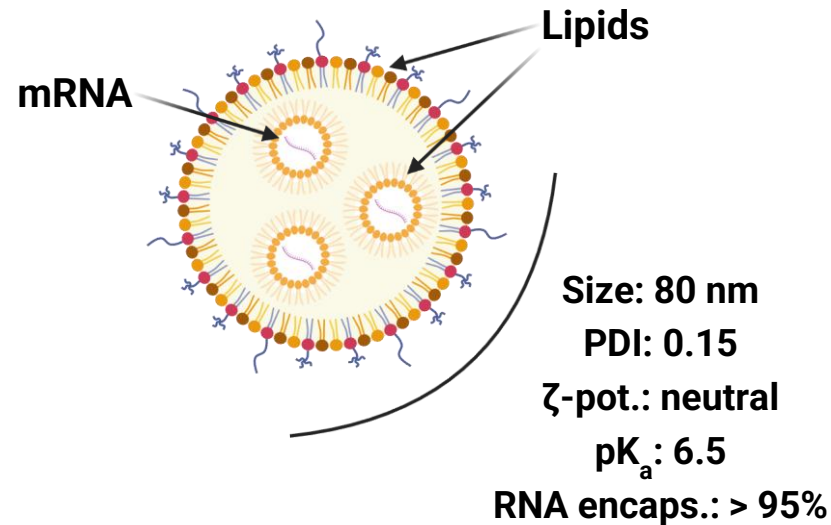


Our solution for unlocking RNA immunotherapy

NC design

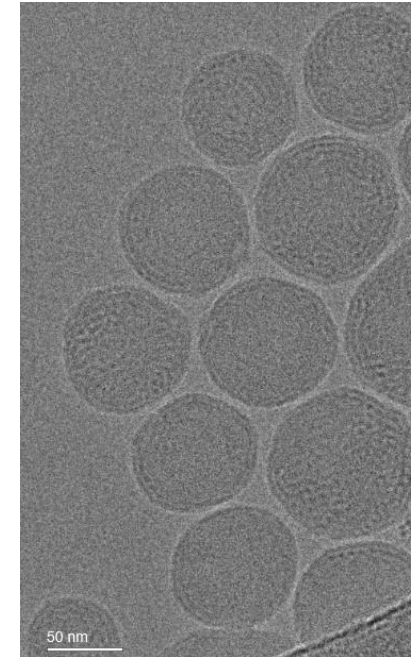


NC characteristics

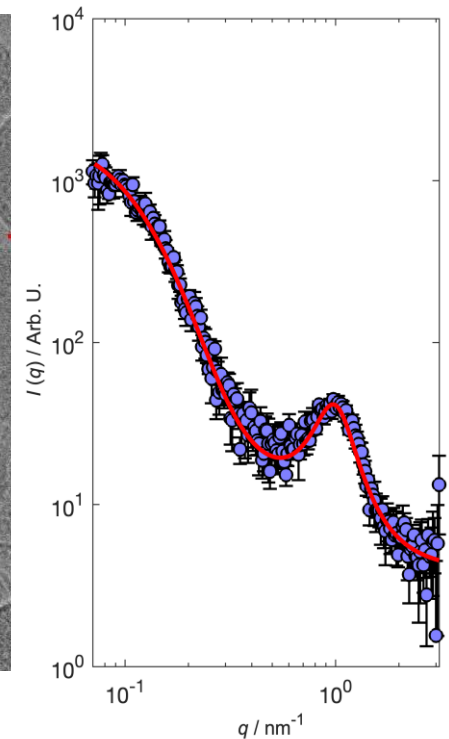


NC structure

cryoTEM

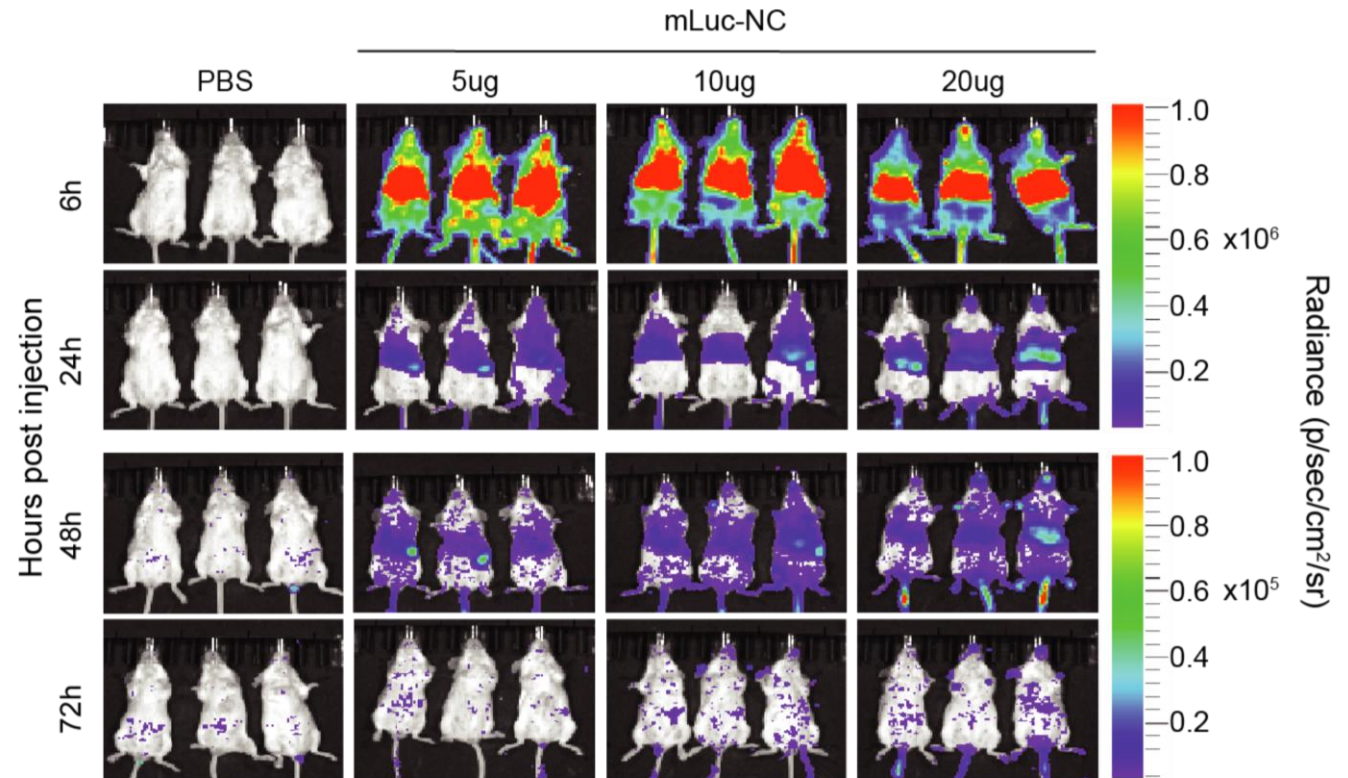
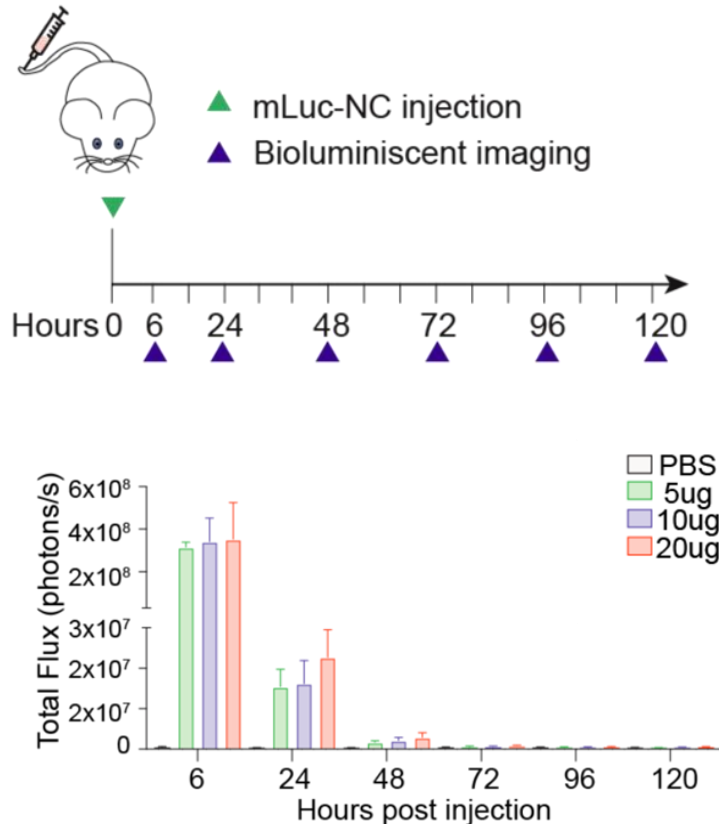


SAXS



mRNA expression and functional biodistribution

BALB/c mice
(n= 3 per group)



mRNA-NC delivery results in functional and transient expression primarily in liver and spleen

In situ production of complex TCEs

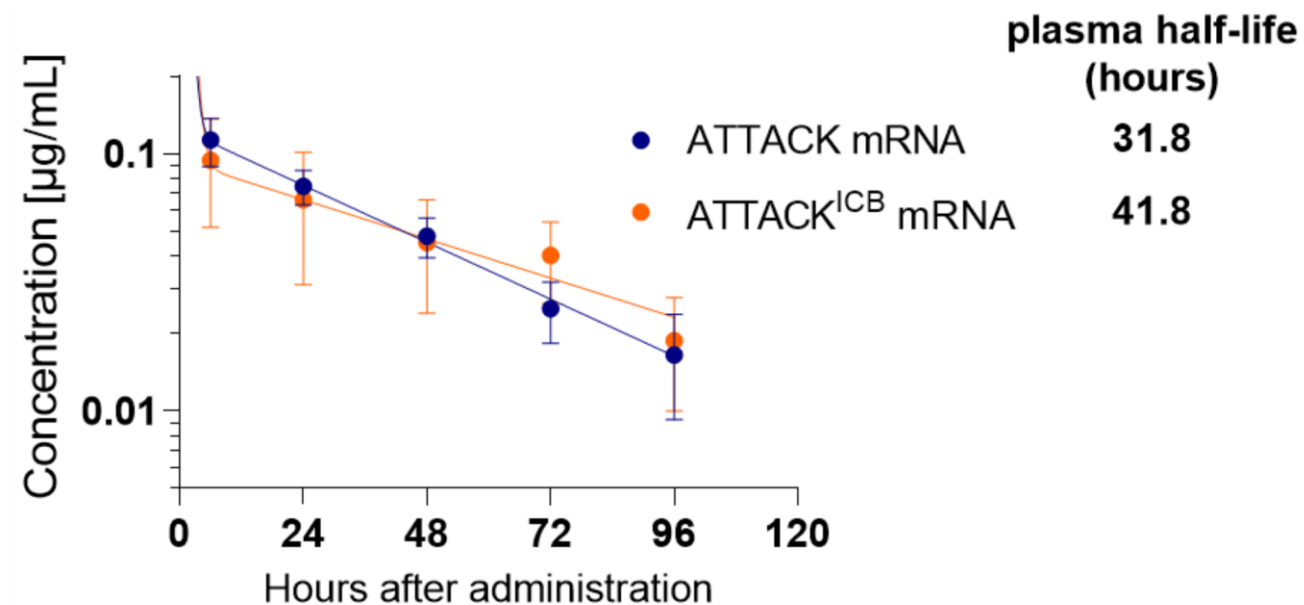
NSG mice
(n= 3 per group)



▲ mATTACK/^{ICB}-NC injection (20 µg)

▲ Blood sampling

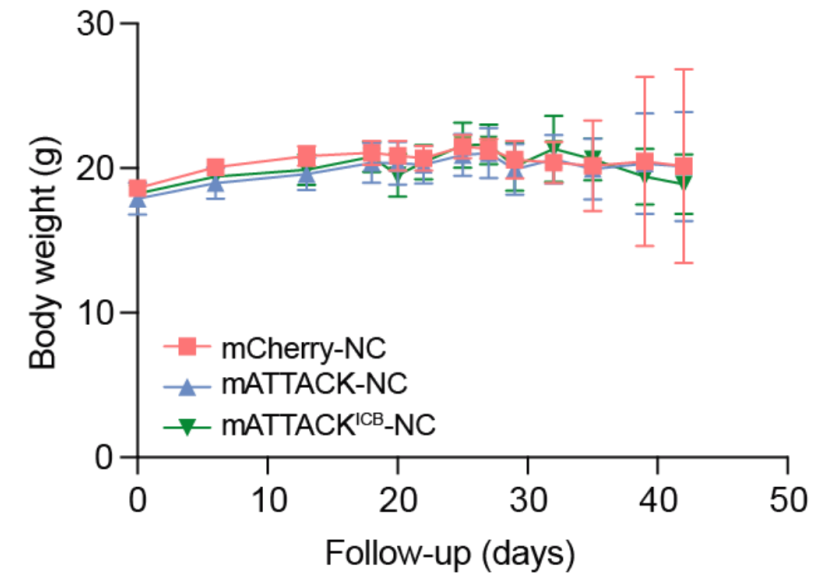
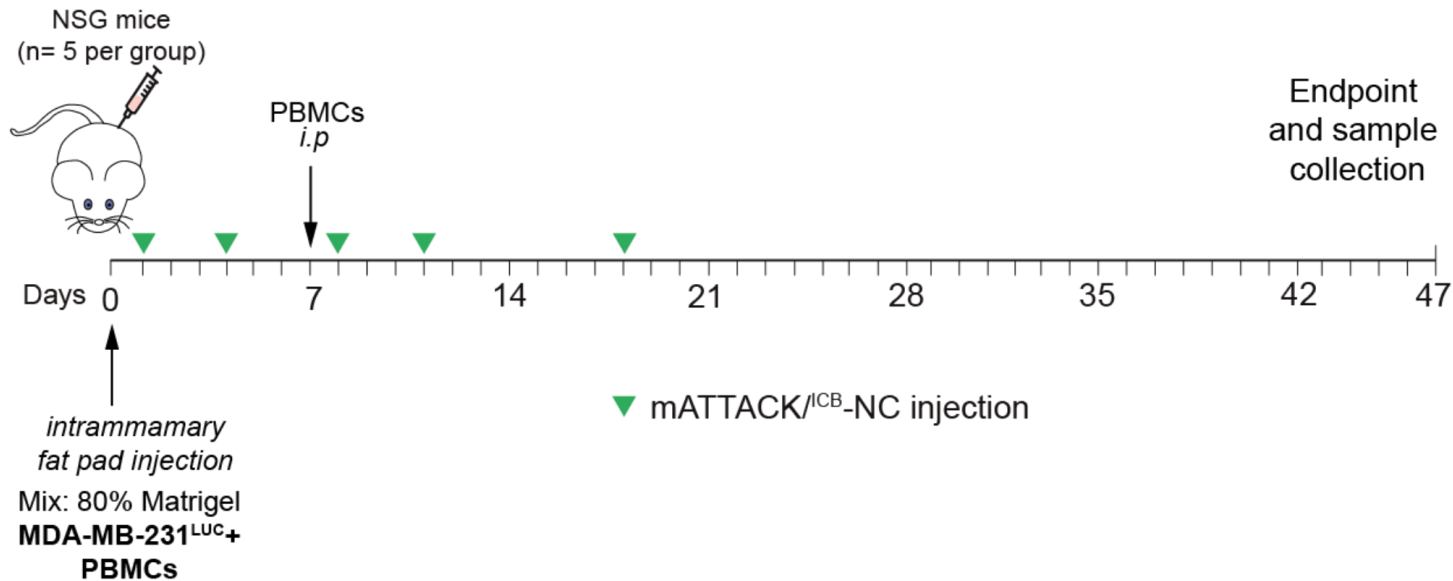
Hours 0 6 24 48 72 96 144 168 216



Systemic mRNA delivery results in expression and secretion of TCEs with promising half-lives

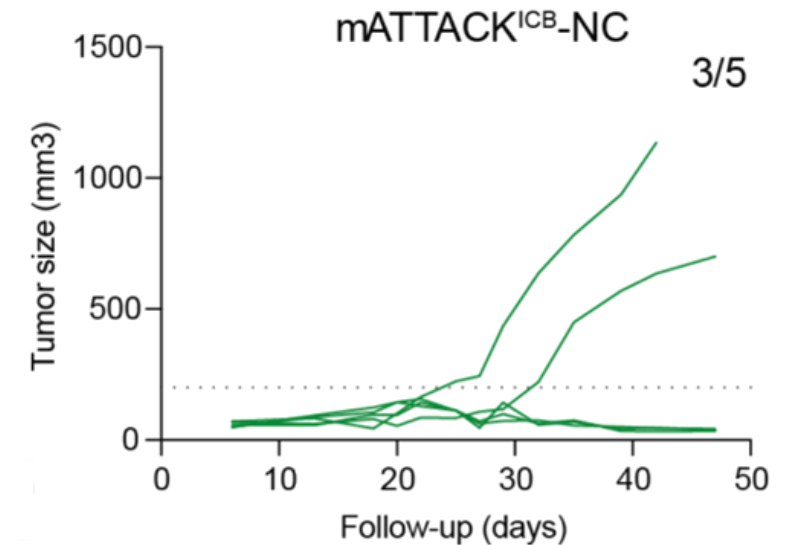
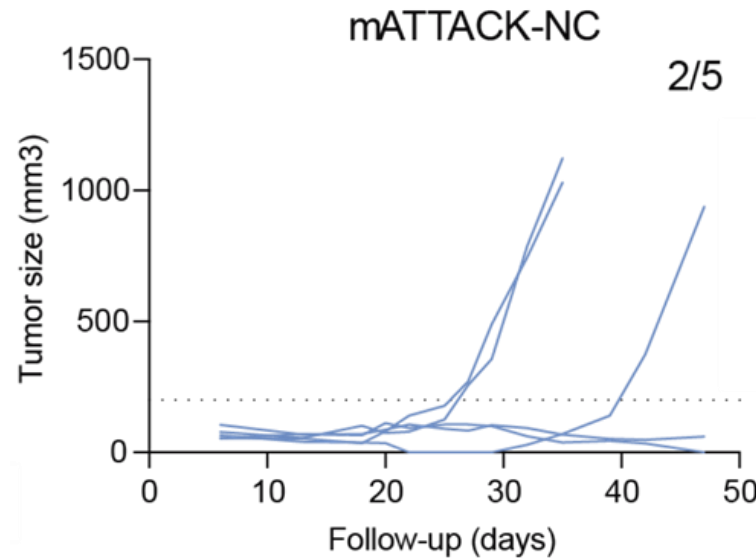
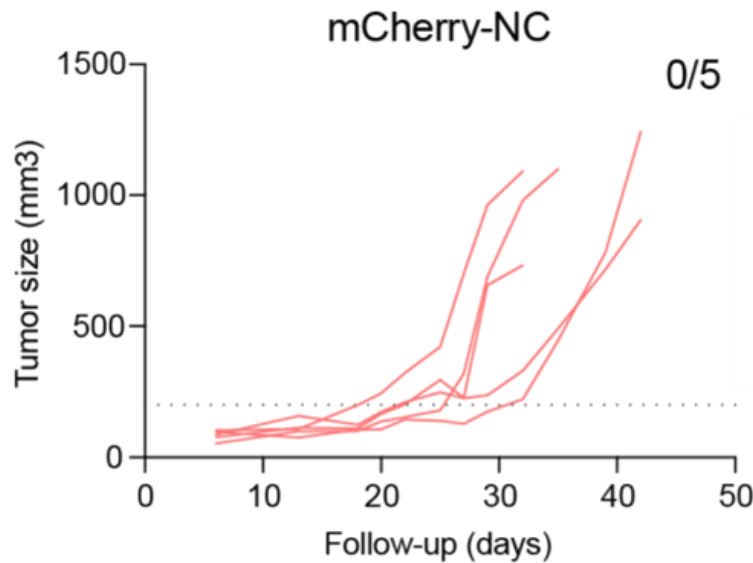
Therapeutic potential of mRNA immunotherapies

Humanized orthotopic breast cancer xenograft model



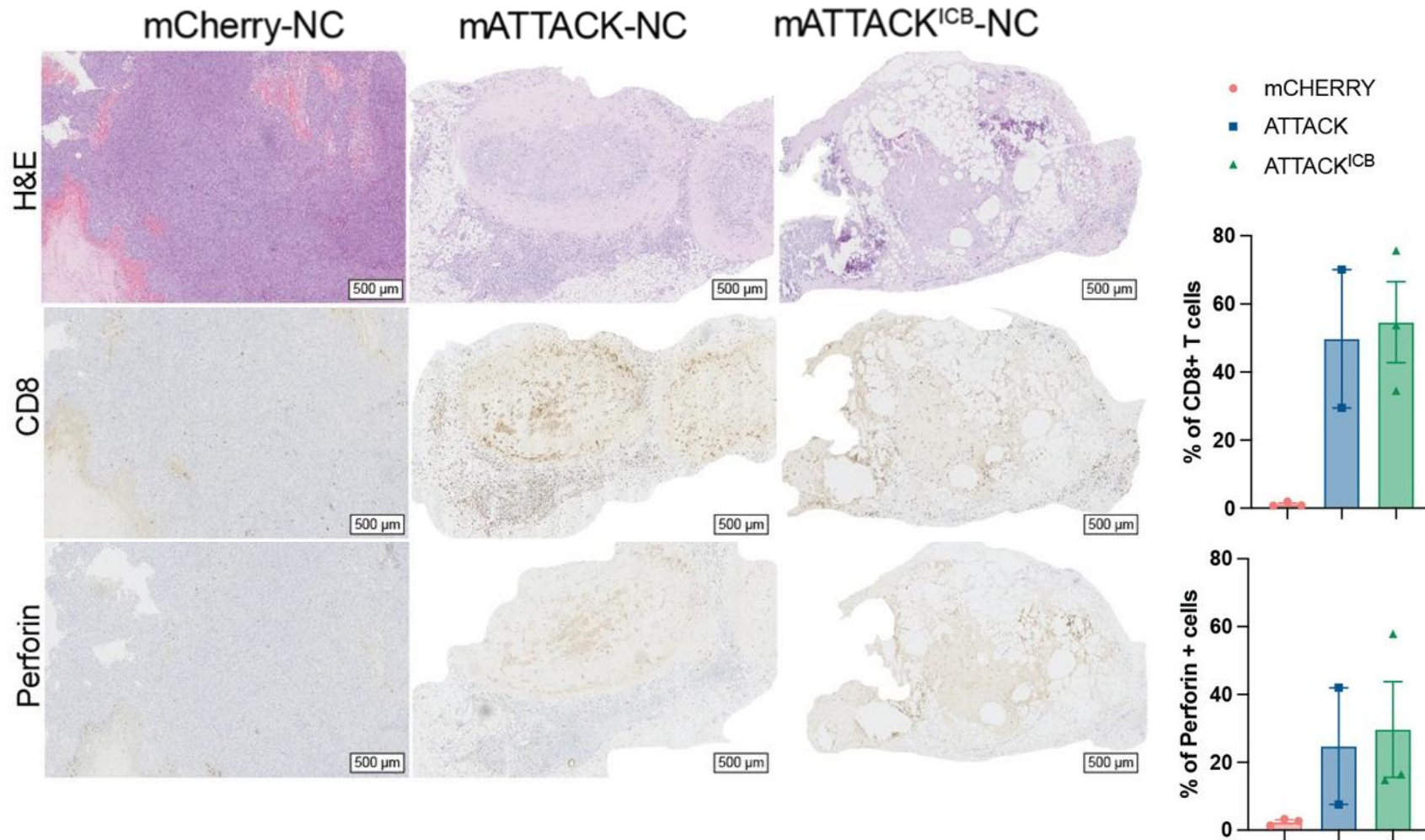
Repeated systemic delivery of NCs was tolerated

Therapeutic potential of mRNA immunotherapies



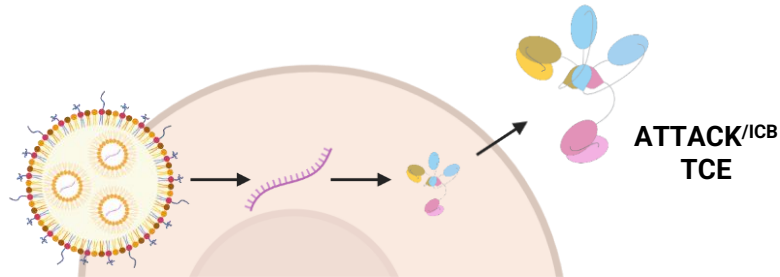
mRNA-TCE delivery results in tumor growth suppression and enhanced survival

Therapeutic potential of mRNA immunotherapies

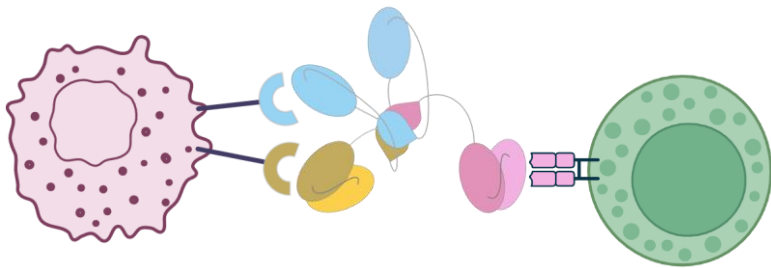


✓ decreased tumor volume and cellular density

Conclusion



- our oil-based NCs functionally deliver large mRNA constructs and allow for transient *in situ* production of complex therapeutic proteins



- the trispecific trimerbody ATTACK^{ICB} enables spatially confined T cell engagement, checkpoint blockade, and tumor targeting

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